

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 18202-028WO1	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/007867	International filing date (day/month/year) 11/03/2005	(Earliest) Priority Date (day/month/year) 12/03/2004
Applicant LIGAND PHARMACEUTICALS INCORPORATED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 11 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box II).

3. ☐ Unity of invention is lacking (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/007867

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1,3-25,28,29,46-51 (all partially),61 (completely),58
62-82 (all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,3-25,28,29,46-51 (all partially), 61 (completely), 58,62-82 (all partially)

Compounds of general formula (I) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82

2. claims: 1-25 (all partially), 26 and 27 (completely), 28 and 29 (partially), 30-38 (all completely), 46-51,58-82 (all partially)

Compounds of general formula (II) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82

3. claims: 1,3-25,28,29,46-51,58 (all partially), 59 and 60 (completely), 62-82 (all partially)

Compounds of general formula (III) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82

4. claims: 1-25,28,29 (all partially), 39-41 (completely), 46-58,62-82 (all partially)

Compounds of general formula (IV) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82

5. claims: 1,3-25,28,29,42 (all partially), 43-45 (completely), 46-51,58,62-82 (all partially)

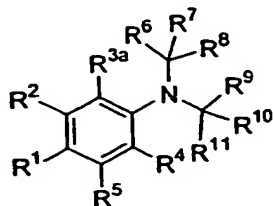
Compounds of general formula (V) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82

6. claims: 1,3-25,28,29,42,46-51 (all partially), 52-57 (completely), 58,62-82 (all partially)

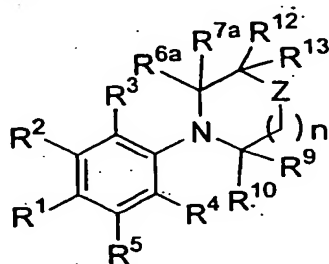
Compounds of general formula (VI) according to claim 1 as well as their pharmaceutical use and compositions according to claims 63-82

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

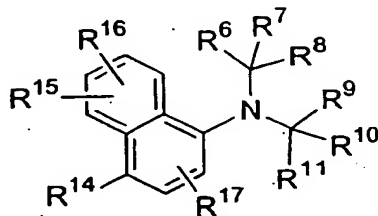
Provided herein are compounds having a structure selected from among Formula I, Formula II, Formula III, Formula IV, Formula V and Formula VI:



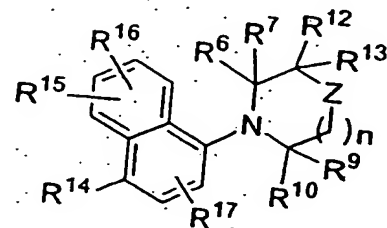
(I)



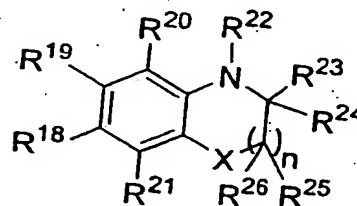
(II)



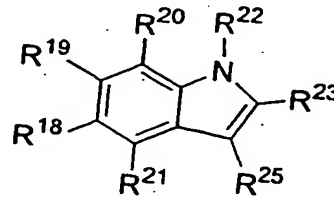
(III)



(IV)



(V)



(VI)

that are androgen receptor modulators and/or androgen receptor binding agents. Also disclosed are methods of making and using such compounds, including, but not limited to, using such compounds for treating various conditions.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/007867

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C211/52 C07C255/58 C07D207/26 C07D207/08 C07D209/12
C07D295/06 C07D211/60 C07D211/22 C07D207/16 C07D207/12
C07D207/09 C07D265/36 C07D209/08 C07D215/18 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI Section Ch, Week 200424 Derwent Publications Ltd., London, GB; Class B02, AN 2004-257164 XP002331455 - & WO 2004/016576 A1 (TAKEDA CHEM IND LTD) 26 February 2004 (2004-02-26) page 230; example 155</p> <p>-----</p>	1-82
X	<p>EP 1 122 242 A (YAMANOUCHI PHARMACEUTICAL CO. LTD) 8 August 2001 (2001-08-08) cited in the application page 39; compounds 1-33 page 1 claims 7,9</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1-82

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

Date of the actual completion of the international search

15 June 2005

Date of mailing of the international search report

05. 08. 2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/007867

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 097 578 A (PERRONNET ET AL) 27 June 1978 (1978-06-27) cited in the application columns 1-2	1-82
X	----- WO 03/011824 A (BRISTOL-MYERS SQUIBB COMPANY; SUN, CHONGQING; ROBL, JEFFREY, A; SALVAT) 13 February 2003 (2003-02-13) cited in the application example 1 claims 7-11	1-82
P,X	----- WO 2005/000795 A (SMITHKLINE BEECHAM CORPORATION; BLANC, JEAN-BAPTISTE, E; CADILLA, RODO) 6 January 2005 (2005-01-06) examples 113,119,120,135 claims 37-42	1-82
X	----- ANLEZARK G M ET AL: "BIOACTIVATION OF DINITROBENZAMIDE MUSTARDS BY AN E.COLI B NITROREDUCTASE" BIOCHEMICAL PHARMACOLOGY, PERGAMON, OXFORD, GB, vol. 50, no. 5, January 1995 (1995-01), pages 609-618, XP000645552 ISSN: 0006-2952 example 1; table 2	1,61,73, 74,78,79
X	----- PANTHANANICKAL, AUGUSTINE ET AL: "Structure-activity relationship of aniline mustards acting against B-16 melanoma in mice" JOURNAL OF MEDICINAL CHEMISTRY, 22(10), 1267-9 CODEN: JMCMAR; ISSN: 0022-2623, 1979, XP002331449 table 1; compound 7	1,61,73, 74,78,79
X	----- GRAVATT, G. LANCE ET AL: "DNA-Directed Alkylating Agents. 6. Synthesis and Antitumor Activity of DNA Minor Groove-Targeted Aniline Mustard Analogs of Pibenzimol (Hoechst 33258)" JOURNAL OF MEDICINAL CHEMISTRY, 37(25), 4338-45 CODEN: JMCMAR; ISSN: 0022-2623, 1994, XP002331450 abstract examples 14,19	1,61
X	----- TURNBULL, KENNETH ET AL: "The reaction of 4-substituted aryl isocyanates with NaBH ₄ /trifluoroacetic acid (TFA)" SYNTHESIS, (3), 391-392 CODEN: SYNTBF; ISSN: 0039-7881, 1999, XP008048153 scheme: compound 3e	1,61
	----- -/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/007867

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NICULESCU-DUVAZ D ET AL: "Self-immolative nitrogen mustard prodrugs for suicide gene therapy" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, no. 26, 17 December 1998 (1998-12-17), pages 5297-5309, XP002265049 ISSN: 0022-2623 compound 49 50	1,61
X	EP 0 711 768 A (MITSUI TOATSU CHEMICALS, INC; MITSUI CHEMICALS, INC) 15 May 1996 (1996-05-15) page 297, line 16 page 315, line 49 page 326, line 3 page 334, line 17 page 339, line 17	1,61
X	PALMER, BRIAN D. ET AL: "Hypoxia-selective antitumor agents. 5. Synthesis of water-soluble nitroaniline mustards with selective cytotoxicity for hypoxic mammalian cells" JOURNAL OF MEDICINAL CHEMISTRY, 35(17), 3214-22 CODEN: JMCMAR; ISSN: 0022-2623, 1992, XP002331451 table 1; compounds 7-10 11-14 examples 2,9,10,13,14	1,61,73, 74,78,79
X	PALMER, B. D. ET AL: "Nitro analogs of chlorambucil as potential hypoxia-selective anti-tumor drugs" ANTI-CANCER DRUG DESIGN, 5(4), 337-49 CODEN: ACDDEA; ISSN: 0266-9536, 1990, XP008048139 table I; compound 3 6 8 examples 4,8,25	1,61
X	PALMER, BRIAN D. ET AL: "Hypoxia-selective antitumor agents. 3. Relationships between structure and cytotoxicity against cultured tumor cells for substituted N,N-bis(2-chloroethyl)anilines" JOURNAL OF MEDICINAL CHEMISTRY, 33(1), 112-21 CODEN: JMCMAR; ISSN: 0022-2623, 1990, XP000609118 examples 5-7; table I	1,61,73, 74,78,79

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/007867

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PRASMICKIENE, G. ET AL: "Synthesis and study of the reactivity of p-[bis(2- chloropropyl)amino]phenylalkanoic acids" XP002331454 retrieved from STN Database accession no. 1969:430178 CAS RN: 23004-87-7 abstract & IZVESTIYA AKADEMII NAUK SSSR,- SERIYA KHIMICHESKAYA , (3), 643-6 CODEN: IASKA6; ISSN: 0002-3353, 1969,</p>	1,61
X	<p>POPP, FRANK D.: "Synthesis of potential anticancer agents. X. Preparation and reactions of aldehydes related to benzaldehyde mustard" JOURNAL OF MEDICINAL CHEMISTRY , 7(2), 210-12 CODEN: JMCMAR; ISSN: 0022-2623, 1964, XP002331453 page 212, column 1 example IX</p>	1,61,73, 74,78,79
X	<p>STEINMAN, MARTIN ET AL: "1-Poly(fluoroalkyl)benzodiazepines" JOURNAL OF MEDICINAL CHEMISTRY , 16(12), 1354-60 CODEN: JMCMAR; ISSN: 0022-2623, 1973, XP002295070 example 12; table I example 17; table II</p>	1,61
X	<p>ABELA MEDICI, ANTHONY J. ET AL: "Cytotoxic compounds. Part 21. Chloro-, methoxy-, and methoxycarbonyl-derivatives of (bis-2-chloroethylamino)-phenols and anilines" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1: ORGANIC AND BIO-ORGANIC CHEMISTRY (1972-1999) , (20), 2258-63 CODEN: JCPRB4; ISSN: 0300-922X, 1977, XP008048335 example 10</p>	1,61,73, 74,78,79
X	<p>US 4 202 895 A (INABA, SHIGEO ET AL) 13 May 1980 (1980-05-13) column 9, line 62 - line 63</p>	1,61
A	<p>WO 02/16310 A (GTX, INC; DALTON, JAMES; MILLER, DUANE, D; YIN, DONGHUA; HE, YALI) 28 February 2002 (2002-02-28) claim 1 examples 1,2</p>	1,61, 63-82

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/007867

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/22432 A (YAMANOUCHI PHARMACEUTICAL CO., LTD; TANIGUCHI, NOBUAKI; OKADA, MINORU;) 28 May 1998 (1998-05-28) abstract page 33 - page 48 -----	1,61, 63-82

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/007867

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004016576	A1	26-02-2004	AU 2003254993 A1 BR 0313405 A CA 2495383 A1 EP 1553074 A1 JP 2004091486 A	03-03-2004 12-07-2005 26-02-2004 13-07-2005 25-03-2004
EP 1122242	A	08-08-2001	AU 754529 B2 AU 5654499 A BR 9914018 A CA 2345146 A1 EP 1122242 A1 JP 3390744 B2 US 2004010037 A1 US 6673799 B1 CN 1129581 C WO 0017163 A1 JP 2003137873 A PL 346795 A1 RU 2221785 C2	21-11-2002 10-04-2000 03-07-2001 30-03-2000 08-08-2001 31-03-2003 15-01-2004 06-01-2004 03-12-2003 30-03-2000 14-05-2003 25-02-2002 20-01-2004
US 4097578	A	27-06-1978	FR 2329276 A1 AU 500542 B2 AU 1909576 A BE 847742 A1 BG 60533 B2 CA 1086751 A1 CH 599164 A5 DE 2649925 A1 DK 487476 A ,B, ES 452746 A1 GB 1518444 A IE 43875 B1 JP 1289956 C JP 52057176 A JP 60011701 B LU 76085 A1 LU 88282 A9 MD 246 B1 NL 930079 I1 NL 7611576 A ,B, SE 430502 B SE 7610859 A SU 596165 A3	27-05-1977 24-05-1979 04-05-1978 28-04-1977 28-07-1995 30-09-1980 12-05-1978 12-05-1977 30-04-1977 01-10-1977 19-07-1978 17-06-1981 14-11-1985 11-05-1977 27-03-1985 31-05-1977 04-05-1994 31-07-1995 16-09-1993 03-05-1977 21-11-1983 30-04-1977 28-02-1978
WO 03011824	A	13-02-2003	EP 1414795 A1 WO 03011824 A1 US 2003055094 A1 US 2004092559 A1	06-05-2004 13-02-2003 20-03-2003 13-05-2004
WO 2005000795	A	06-01-2005	WO 2005000795 A2	06-01-2005
EP 0711768	A	15-05-1996	CA 2168016 A1 DE 69525418 D1 DE 69525418 T2 EP 0711768 A1 US 5852011 A ES 2172585 T3 WO 9532960 A1	07-12-1995 21-03-2002 17-10-2002 15-05-1996 22-12-1998 01-10-2002 07-12-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/007867

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 0711768	A		JP	3258531 B2		18-02-2002
			JP	9003065 A		07-01-1997
			KR	172649 B1		01-02-1999

US 4202895	A	13-05-1980	NONE			

WO 0216310	A	28-02-2002	AU	8523001 A		04-03-2002
			BR	0114801 A		14-10-2003
			CA	2420279 A1		28-02-2002
			CN	1471508 A		28-01-2004
			EP	1401801 A1		31-03-2004
			EP	1491524 A2		29-12-2004
			JP	2004518617 T		24-06-2004
			WO	0216310 A1		28-02-2002
			US	2002099036 A1		25-07-2002
			US	2002099096 A1		25-07-2002
			US	2002173495 A1		21-11-2002
			US	2003022868 A1		30-01-2003
			US	2003162761 A1		28-08-2003
			US	2003232792 A1		18-12-2003
			US	2003225040 A1		04-12-2003
			US	2004014975 A1		22-01-2004
			US	2004260108 A1		23-12-2004
			US	2005038110 A1		17-02-2005

WO 9822432	A	28-05-1998	AU	4966497 A		10-06-1998
			WO	9822432 A1		28-05-1998
